REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of formal nature, and do not add new matter.

Prior to the present amendment, Claims 58-70 were pending in this application and were rejected on various grounds. With this amendment, Claims 66-67 have been canceled without prejudice and Claims 58-65 have been amended to clarify what Applicants have always regarded as their invention.

Accordingly, Claims 58-65, 68-70 are pending after entry of the instant amendment. Support for the amendments to Claims 58-65 can be found throughout the specification, particularly at page 347, line 28 to page 348, line 5. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

Applicants submit that having reviewed the application, Applicants have found that as a result of the present claim amendments, fewer than all of the currently named inventors are the actual inventors of the invention being claimed in the present application. Accordingly, an Amendment Under 37 C.F.R. § 1.48(b) amending inventorship is enclosed with this response.

Priority

The Examiner has asserted that the earliest priority date available for the instant application is October 1, 2001 based on the preliminary amendment submitted on 12-29-03. Applicants respectfully disagree with the Examiner's determination of priority.

Applicants respectfully direct Examiner's attention to the Preliminary Amendment filed on August 21, 2002.

Applicants rely on the glucose/FFA uptake assay (Example 117, Assay 94) for patentable utility which was first disclosed in PCT/US00/04341 filed on February 18, 2000, priority to which has been claimed in this application. Accordingly, the present application is entitled to at

least the February 18, 2000 priority for subject matter defined in Claims 58-65, 68-70 and 74-77. In support, Applicants enclose herewith pages 355-356 of the PCT Publication WO 00/53756, corresponding to PCT Application PCT/US00/04341.

Specification

As requested by the Examiner, the title of the application has been amended to recite a new, descriptive title indicative of the invention to which the claims are directed.

In addition, the specification has been amended to remove embedded hyperlink and/or other form of browser-executable code.

Further, Applicants have amended the specification to clearly recite the conditions of the deposits made under the Budapest Treaty.

Claim Rejections – 35 U.S.C. §101

Claims 58-70 stand rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well-established utility." (See page 3 of the instant Office Action).

Claims 66-67 have been canceled, thereby rendering their rejection moot. Applicants submit, as discussed below, that not only has the PTO not established a *prima facie* case for lack of utility, but that Claims 58-65 and 68-70 possess a specific and substantial asserted utility.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, **any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient**, at least with regard to defining a "'substantial'" utility.'" (M.P.E.P. §2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. §2107 II (B) (1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." (M.P.E.P. §2107 II (B) (1) (ii)) Such a standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

Utility – Application of Standard

As discussed above, Applicants rely on the adipocyte glucose/FFA uptake assay (Example 117, Assay #94) for support of patentable utility. This assay was first disclosed in

International Application Serial No. PCT/US00/04341, filed on February 18, 2000, the priority of which is claimed in the present application.

The adipocyte glucose/FFA uptake assay is designed to determine whether a polypeptide is capable of modulating, either positively or negatively, the uptake of glucose or free fatty acids in adipocyte cells. By making such determinations, the assay identifies polypeptides that are expected to be useful for treating disorders wherein stimulation or inhibition of glucose uptake by adipocytes is expected to be therapeutically effective. Examples of these types of disorders include obesity, diabetes, and hyper- or hypo-insulinemia.

The adipocyte glucose/FFA assay is performed as follows: primary rat adipocyte cells are plated on a 96 well plate and incubated overnight with media supplemented with PRO195 polypeptide. After the initial overnight incubation, samples of the media are taken at hour 4 and hour 16 and residual glycerol, glucose and FFA are measured. After the hour 16 sample is taken, insulin is added to the media and the adipocytes are allowed to incubate for an additional 4 hours. After this final 4 hour incubation, another sample is taken and residual glycerol, glucose and FFA is measured again. As a control, identical incubations and samplings are performed on cells that have been incubated overnight in media initially supplemented with insulin rather than PRO195 polypeptide. Results are scored as positive in the assay if the uptake is greater than 1.5 times (stimulatory) or less than 0.5 time (inhibitory) the uptake of the insulin control. As PRO195 resulted in less than 0.5 the uptake of the insulin control, PRO195 tested positive as an inhibitor of glucose/FFA uptake in adipocyte cells.

The glucose/FFA uptake assay as described in Example 117 of the instant application was also well known in the art at the time of the effective filing date of the instant application. Similar assays were commonly used to identify potential anti-diabetic agents and study the regulatory mechanisms of important molecules involved in fat cell metabolism.

For example, at the time of the effective filing date of the instant application, it was well known in the art that increasing glucose uptake by adipocyte cells is a hallmark of a number of therapeutically effective agents, such as troglitazone and poiglitazone. (Tafuri, *Endocrinology*,

137(11): 4706-4712 (1996); Sandouk, *et al., Endocrinology*, 133(1):352-359 (1993) - copies enclosed). Both troglitazone and poiglitazone are members of the thiazolidinedione class of compounds and have been used to effectively treat noninusulin-dependent diabetes mellitus (NIDDM), the most common form of diabetes. Both compounds function, at least in part, by increasing the number of cellular glucose transporters in order to facilitate increased glucose uptake.

Further, at the time of the effective filing date of the instant application, vanadium salts were considered as a possible treatment for diabetes, and several clinical trials had already been performed. (page 26617, right column, Goldwaser *et al., J. Biol Chem.*, 274(37):26617-26624 (1999) - copy enclosed). Using the rat adipocyte culture system similar to the system disclosed in the instant application, Goldwaser *et al.*, showed that vanadium ligand l-Glu (γ)HXM potentiates the capacity of free vanadium ions to activate glucose uptake and glucose metabolism in rat adipocytes *in vitro* by 4-5 folds and to lower blood glucose levels in hyperglycemic rats *in vivo* by 5-7 folds. This is further evidence that at the effective filing date of the present application one skilled in the art would have reasonably expected that molecules activating glucose uptake would find utility in the treatment of diabetes and related diseases.

In addition, the investigators in Mueller *et al.*, who were interested in determining the influence of glucose uptake on leptin secretion, employed essentially the same assay to measure changes in glucose uptake after insulin exposure. (Mueller *et al., Endocrinology*, 139(2): 551-558 (1998) - copy enclosed). Figure 1A shows the glucose concentrations in medium from 0-96 hours from isolated rat adipocytes in primary culture with various insulin concentrations. As indicated by the decrease in glucose in the medium in the Figure, Mueller *et al.* suggest that insulin produced a concentration-dependent increase in glucose uptake by the cultured adipocytes. Based on these experimental results, the authors stated that insulin increased leptin secretion over 96 hours, and the increase in leptin was closely related to the amount of glucose taken up by the adipocytes than to the insulin concentration, suggesting a role for glucose transport and/or metabolism in regulating leptin secretion. (See Abstract).

Using the same assay system, Mueller *et al.* further studied the effect on leptin secretion of two well-known anti-diabetic agents, metformin and vanadium, which were known to enhance the glucose uptake. (Muller *et al.*, *Obesity Research,* 8(7): 530-539 (2000) - copy enclosed). The experimental data indicated that both metformin and vanadium increased glucose uptake and inhibit leptin secretion from cultured adipocytes.

Accordingly, Applicants respectfully submit that at the effective filing date of the instant application, one of skill in the art would have reasonably accepted that various compounds, such as PRO195, that are capable of modulating glucose uptake have a substantial, practical, real life utility. The above-mentioned studies have clearly established that the glucose/FFA uptake assay as described in the instant application is a reliable assay system to identify the therapeutic agents for treating diseases and conditions such as obesity, diabetes, hyper- or hypo-insulinemia. Therefore, Applicants respectfully submit that a variety of real-life utilities, such as treatments for glucose uptake related diseases, including obesity and diabetes, are envisioned for PRO195 based on the glucose/FFA uptake assay results disclosed herein.

In view of the above, Applicants respectfully submit that the specification discloses at least one credible, substantial and specific asserted utility for the polypeptide PRO195. Accordingly, the Examiner is requested to reconsider and withdraw the present rejection under 35 U.S.C. §101.

Claim Rejections – 35 U.S.C. §112, First Paragraph (Written Description)

Claims 58-70 are rejected under 35 U.S.C. §112, first paragraph, for allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claimed invention." In particular, the Examiner notes that "the claims as written include polypeptides having at least 80-99% sequence identity with SEQ ID NO:330 and polypeptides including or lacking various regions including, lacking its signal peptide, the extracellular domain, the extracellular domain but lacking its signal peptide, but for which no particular biological activity or function is recited." Therefore the Examiner asserts that "the

instant disclosure of a single polypeptide, that of SEQ ID NO:330 with the instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera."

Applicants submit that the cancellation of Claims 66-67 renders the rejection of those claims moot.

Without acquiescing to the Examiner's position, and solely in the interest of expediting prosecution in this case, Claims 58-62 (and, as a consequence, those claims dependent from the same) are amended to recite "the polypeptide inhibits the uptake of glucose or FFA (free fatty acid) by adipocyte cells." Accordingly, the claims are no longer drawn to a genus of polypeptides defined by sequence identity alone. The recited biological activity, coupled with a well defined, and relatively high degree of sequence identity are believed to sufficiently define the claimed genus, such that one skilled in the art would readily recognize that the Applicants were in the possession of the invention claimed at the effective filing date of this application. The Examiner is therefore respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 58-70 stand rejected under 35 USC § 112, first paragraph, as failing to enable a person of skill in the art to make and use the invention commensurate in scope with the claims. In particular, the Examiner asserts that "the specification does not reasonably provide enablement for the variable peptide sequences and for such generic sequences where no requisite functional activity is provided as claimed." (See page 9 of the instant Office Action.)

Applicants submit that the cancellation of Claims 66-67 renders the rejection of those claims moot.

While not acquiescing in the propriety of this rejection of the currently pending claims, and solely in the interest of furthering prosecution, Applicants have amended Claims 58-62 (and, as a consequence, those claims dependent from the same) to recite, "wherein the polypeptide

inhibits the uptake of glucose or FFA (free fatty acid) by adipocyte cells." Since the claimed genus is now characterized by a combination of structural and functional features, any person of skill would know how to make and use the invention without undue experimentation based on the general knowledge in the art at the time the invention was made. As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" *In re Certain Limited-charge cell Culture Microcarriers, 221 USPQ 1165, 1174* (Int'l Trade Comm'n 1983), *aff'. sub nom., Massachusetts Institute of Technology v A.B. Fortia,* 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985) M.P.E.P. 2164.01. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claims 58-70 are further rejected under 35 U.S.C. §112, first paragraph, allegedly for containing "subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." The Examiner further asserts that "the specification lacks complete deposit information for the deposit of ATCC 209772."

Applicants submit that the cancellation of Claims 66-67 renders the rejection of these claims moot.

In addition, Applicants disagree with the Examiner's assertion that the deposit was necessary for enablement of the current invention. The current invention is fully enabled by the disclosure of the present application, including the sequence of PRO195 and its coding sequence. Further, as discussed above, the foregoing amendment to the specification corrects the address of ATCC, and further elaborates on the conditions of the deposit, which was made for patent purposes, under the terms of the Budapest treaty.

Nevertheless, Applicants enclose herewith a copy of the deposit receipt indicating that DNA56405-1357 deposit, ATCC Deposit No. 209772, was made by Applicants on April 14, 1998.

In addition, as stated above, Applicants respectfully submit that the specification clearly discloses that the deposit was made under the Budapest Treaty and provides the accession number for the deposit, the date of the deposit, the description of the deposited material, and the name and address of the depository starting on page 372, line 34 of the specification.

Applicants further submit that the specification has been amended to recite that the deposit will be maintained "for 30 years from the date of deposit and for at least five (5) years after the most recent request for the furnishing of a sample of the deposit received by the depository" and to recite that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent."

Accordingly, Applicants believe that the present rejection should be withdrawn.

Claim Rejections – 35 USC § 112, Second Paragraph

Claims 58-70 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants submit that the cancellation of Claims 66-67 renders the rejection of these claims moot.

Without acquiescing to the Examiner's position, and solely in the interest of expediting prosecution in this case, as amended, the terms "extracellular domain" and "extracellular domain … lacking its associated signal peptide" are no longer present in Claims 58-63 (and, as a consequence, those claims dependent from the same). Hence, the rejection is believed to be moot, and should be withdrawn.

Claim Rejections – 35 USC § 102

Claims 58-70 are rejected under 35 U.S.C. § 102(e) as anticipated by Furness *et al.*, (U.S. Patent No. 6,673,549, issued January 6, 2004), allegedly because Furness *et al.* disclose a polypeptide (SEQ ID NO:818) having 100% identity to that of SEQ ID NO:330.

Applicants respectfully disagree and traverse this rejection.

Applicants submit that the cancellation of Claims 66-67 renders the rejection of these claims moot.

As discussed above, Applicants are entitled to an effective filing date of February 8, 2000. Furness *et al.* claims benefit of U.S. Provisional Application, No. 60/240,409 filed on October 12, 2000. Therefore, the earliest possible priority date for Furness *et al.* is October 12, 2000, which is well after the priority date of the instant application Accordingly, Applicants submit that Furness *et al.* is not prior art under 102(e) since its filing date and/or effective priority date is after the effective priority date of this application. Therefore, the Examiner is respectfully requested to reconsider and withdraw the rejection under 35 U.S.C. §102(e).

Reference by Tang *et al.*

Applicants respectfully submit and request the consideration of International PCT Application No. PCT/US99/11904, PCT Publication WO 99/61471. The publication date of Tang *et al.* is December 2, 1999.

In response to an anticipated 102(a) rejection over Tang *et al.* Applicants respectfully submit Declaration under 37 C.F.R. §1.131 by Dr. Baker, Dr. Gurney and Dr. Stewart, which establishes that Applicants had cloned and sequenced PRO195 before the Tang *et al.*'s publication date of December 2, 1999. The consideration of the Declarations is respectfully requested.

Applicants respectfully submit that an executed copy of the Declaration will be submitted to the Examiner shortly.

U.S. Provisional Application Serial No. 60/081,817 Simply Needs to Disclose What is Disclosed in the Cited Reference to Support the Priority Claim

Applicants respectfully submit that in order to overcome the 35 U.S.C. §102(a) rejection over Tang *et al.* and support the priority claim, the Declarations by Dr. Baker, Dr. Gurney and Dr. Stewart ("Declarations") simply need to provide a disclosure commensurate in scope with the disclosure in the prior art document by Tang *et al.*

In order to remove a reference as a prior art, "[i]t is sufficient if [the affidavit under Patent Office Rule 131] shows that as much of the claimed invention as is taught in the reference has been reduced to practice by the [patentee] prior to the date of the reference." *In re* Stempel, 241 F.2d 755, 757 (1957). In *In re* Stempel, the patent applicant (Stempel) had claims directed to both (i) a particular genus of chemical compounds (the "generic" claim) and (ii) a single species of chemical compound that was encompassed within that genus (the "species" claim). In support of a rejection under 35 U.S.C. §102, the examiner cited against the application a prior art reference that disclosed the exact chemical compound recited in the "species" claim. In response to the rejection, the patent applicant filed a declaration under 37 C.F.R. §1.131 demonstrating that he had made that specific chemical compound prior to the effective date of the cited prior art reference. The Court found the applicant's 37 C.F.R. § 1.131 declaration effective for swearing behind the cited reference for purposes of both the "species" claim and the "genus" claim. Specifically, the Court stated in support of its decision that "**all the applicant can be required to show is priority with respect to so much of the claimed invention as the reference happens to show.** When he has done that he has disposed of the reference." *Id.* at 759.

Furthermore, the Examiner is respectfully directed to *In re* Moore, 170 USPQ 260 (CCPA 1971), where the holding in *In re* Stempel was affirmed. In *In re* Moore, the patent applicant claimed a particular chemical compound in his patent application and the examiner cited against the applicant a prior art reference under 35 U.S.C. §102 rejection which disclosed the compound but did not disclose any specific utility for the compound. The patent applicant filed a declaration under 37 C.F.R. §1.131 demonstrating that he had made the claimed

compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. On appeal, the Court indicated that the 131 declaration filed by the patent applicant was sufficient to remove the cited reference. The Court relied on the established "Stempel Doctrine" to support its decision, stating:

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference ... the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes.

In re Moore, 170 USPQ at 267 (emphasis added).

Thus, *In re* Moore confirmed the holding in *In re* Stempel which states that in order to effectively remove a cited reference with a declaration under 37 C.F.R. §1.131, an applicant need **only show that portion of his or her claimed invention that appears in the cited reference**.

Tang *et al.* discloses a number of human transmembrane proteins, "HTMPN", including a polypeptide sequence SEQ ID NO:63, designated HTMPN-63, that has 100% sequence identity to SEQ ID NO: 330 of the present application. Although Tang *et al.* discloses a list of diseases/conditions that may be associated with the tissues expressing the polypeptide encoded by SEQ ID NO:142, it is devoid of any experimental data to support such utility. Therefore, Applicant's respectfully submit that such disclosure, without additional teaching, does not confer utility (see Table 3 of Tang *et al.*, page 115). Further, as the Examiner has noted on page 5 of the instant Office Action, Applicants have disclosed that PRO195 was tested positive in the stimulation of heart neonatal hypertrophy assay (Assay 1, Example 119), which was first disclosed in Provisional Application 60/145,698, filed 7/26/1999, which precedes by over four months, the publication date of Tang *et al.* (December 2, 1999). (See Provisional Application 60/145,698, Example 43, pages 292-293). In addition, Applicants further submit that PRO195

was tested positive in the stimulation of heart neonatal hypertrophy induced by F2a assay (Assay 37, Example 120), which was first disclosed PCT Application PCT/US99/28313, filed 11/30/1999. Therefore, if the Examiner is to assert that Tang *et al.* provides the slightest indication of utility based on the disclosures in Tables 2 and 3, then the Applicants respectfully submit that Applicants have disclosed at least to the same extent, if not greater, the potential utility for the claimed polynucleotides at an earlier date.

Accordingly, Applicants respectfully submit that since Tang *et al.* only discloses a polypeptide sequence and its encoding nucleic acid sequence (see Table 2 and Table 3) without any disclosure to support utility, the Declaration simply needs to show possession of the polypeptide sequence and its encoding polynucleotide sequence as disclosed in Tang *et al.* in order to overcome the 35 U.S.C. §102 rejection.

Applicants respectfully submit that U.S. Provisional Application No. 60/081,817, filed on April 15, 1998, provides the nucleic acid and amino acid sequences of the PRO195 polypeptide (see U.S. Provisional Application No. 60/081,817, SEQ ID NO:1 and SEQ ID NO:3, respectively).

The Declaration clearly states that U.S. Provisional Application No. 60/081,817, filed on April 15, 1998, discloses sequences designated as SEQ ID NO:1 and SEQ ID NO:3, which are identical to SEQ ID NO:329 and SEQ ID NO:330, respectively, of the instant application.

Accordingly, Applicants respectfully submit that the disclosures are commensurate in scope and that U.S. Provisional Application No. 60/081,817, filed on April 15, 1998, discloses all that the cited prior art discloses.

Consequently, based on the holdings of *In re* Stempel and *In re* Moore, Applicants respectfully submit that Tang *et al.* is not prior art under 102(a) since its publication date is after the invention by the Applicants for patent. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of Claims 58-65 and 68-70 under 35 U.S.C. §102(a).

CONCLUSION

All claims pending in the present application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39780-2630 P1C3**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: December 30, 2004

By: _____
Anna L. Barry (Reg. No. 51,436)

HELLER EHRMAN WHITE & McAULIFFE LLP
275 Middlefield Road
Menlo Park, California 94025-3506
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 2053688 v1
12/30/04 10:34 AM (39780.2630)